

## TRANSMITTAL LETTER TO THE UNITED STATES

DESIGNATED/ELECTED OFFICE (DO/EO/US)

CONCERNING A FILING UNDER 35 U.S.C. 371

VI/98-023.DE.PCT.US

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/763646

INTERNATIONAL APPLICATION NO.

PCT/EP99/06290 ✓

INTERNATIONAL FILING DATE

26/08/1999 ✓

PRIORITY DATE CLAIMED

28/08/1998 ✓

TITLE OF INVENTION

SYRINGES AND INJECTORS INCORPORATING MECHANICAL FLUID AGITATION DEVICES ✓

APPLICANT(S) FOR DO/EO/US

URICH KLAUS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
- a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
- b. ☒ has been transmitted by the International Bureau.
- c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
- a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
- b. ☐ have been transmitted by the International Bureau.
- c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
- d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

## Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Form PCT/IB/308

U.S. APPLICATION NO. 09/763648

INTERNATIONAL APPLICATION NO.

A1

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PCT/EP99/06290

VI/98-023.DE.PCT.US

21. The following fees are submitted:

**BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5) ) :**

- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1,000.00
- ☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$860.00
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$710.00
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$690.00
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$100.00

**ENTER APPROPRIATE BASIC FEE AMOUNT =****CALCULATIONS PTO USE ONLY****\$860.00**Surcharge of **\$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).**\$0.00**

| CLAIMS             | NUMBER FILED | NUMBER EXTRA | RATE      |
|--------------------|--------------|--------------|-----------|
| Total claims       | 111 - 20 =   | 91           | x \$18.00 |
| Independent claims | 9 - 3 =      | 6            | x \$80.00 |

**\$1,638.00****\$480.00**Multiple Dependent Claims (check if applicable). ☒**\$270.00****TOTAL OF ABOVE CALCULATIONS =****\$3,248.00**Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable). ☐**\$0.00****SUBTOTAL =****\$3,248.00**Processing fee of **\$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).**\$0.00****TOTAL NATIONAL FEE =****\$3,248.00**Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). ☐**\$0.00****TOTAL FEES ENCLOSED =****\$3,248.00**

|               |    |
|---------------|----|
| Amount to be: | \$ |
| refunded      |    |
| charged       | \$ |

A check in the amount of \_\_\_\_\_ to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **13-2530** in the amount of **\$3,248.00** to cover the above fees.  
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **13-2530** A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

Gregory L. Bradley  
Medrad, Inc.  
One Medrad Drive  
Indianola, PA 15051

SIGNATURE

Gregory L. Bradley

NAME

34,299

REGISTRATION NUMBER

February 26, 2001

DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
KLAUS URICH )  
Serial No.: Unassigned )  
Filed: Herewith )  
For: SYRINGES AND INJECTORS )  
INCORPORATING MECHANICAL FLUID )  
AGITATION DEVICES )

PRELIMINARY AMENDMENT

Assistant Commissioner  
for Patents  
Box PCT  
Washington, D.C. 20231

Dear Sir:

Please enter the following amendments in the above-identified application  
before the examination thereof. An appendix containing the pending claims – Claims  
1-33 and 34-111 – is attached.

In the Claims:

Please add the following new claims:

-- 34. A syringe for use with an injector having a movement mechanism  
operably associated therewith, the syringe comprising:  
a body comprising a distal discharge end;  
a plunger movably disposed within the body; and  
at least one agitation element disposed within the body between the plunger  
and the distal discharge end, the at least one agitation element operable to agitate a  
fluid in the syringe when the syringe is rotated by means of the movement mechanism.

35. The syringe of Claim 34 wherein the fluid comprises a contrast agent.

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36. The syringe of Claim 35 wherein the contrast agent comprises an ultrasound contrast agent.

37. The syringe of Claim 34 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

38. The syringe of Claim 34 wherein the at least one agitation element comprises a solid.

39. The syringe of Claim 38 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

40. The syringe of Claim 34 wherein the at least one agitation element comprises a gas.

41. The syringe of Claim 34 wherein the movement mechanism operably associated with the injector is further operable to move the syringe in one or more of circular, partially circular and linear motions.

42. The syringe of Claim 34 wherein the axis of rotation is variable.

43. The syringe of Claim 34 wherein the at least one agitation element comprises a casing.

44. The syringe of Claim 40 wherein the at least one agitation element is surrounded by a cover.

45. The syringe of Claim 34, further comprising a recess defined in at least one of the body of the syringe and the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

46. The syringe of Claim 45 wherein the recess is defined in the body of the syringe adjacent to the distal discharge end thereof.

47. The syringe of Claim 45 wherein the recess is defined in the plunger of the syringe.

48. The syringe of Claim 45 wherein the recess comprises an annular recess.

49. A syringe for use with an injector having a movement mechanism operably associated therewith, the syringe comprising:

a body comprising a distal discharge end;

a plunger movably disposed within the body;

at least one agitation element disposed within the body between the plunger and the distal discharge end, the at least one agitation element operable to agitate a fluid in the syringe when the syringe is moved with respect to gravity by means of the movement mechanism; and

a recess defined in the body of the syringe, the recess operable to accommodate the at least one agitation element.

50. The syringe of Claim 49 wherein the fluid comprises a contrast agent.

51. The syringe of Claim 50 wherein the contrast agent comprises an ultrasound contrast agent.

52. The syringe of Claim 49 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

53. The syringe of Claim 49 wherein the at least one agitation element comprises a solid.

54. The syringe of Claim 53 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

55. The syringe of Claim 49 wherein the at least one agitation element comprises a gas.

56. The syringe of Claim 49 wherein the movement mechanism operably associated with the injector is operable to move the syringe in one or more of circular, partially circular and linear motions.

57. The syringe of Claim 49 wherein the movement mechanism operably associated with the injector is operable to move the syringe in a rotational motion.

58. The syringe of Claim 57 wherein the axis of rotation is variable.

59. The syringe of Claim 49 wherein the at least one agitation element comprises a casing.

60. The syringe of Claim 55 wherein the at least one agitation element is surrounded by a cover.

61. The syringe of Claim 49 wherein the recess comprises an annular recess.

62. An injector system comprising:  
an injector comprising a syringe mounting device;  
a syringe comprising:

a body comprising a distal discharge end and an injector attachment device cooperable with the syringe mounting device for mounting the syringe on the injector;

a plunger movably disposed within the body; and

at least one agitation element disposed within the body between the plunger and the distal discharge end; and

a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe.

63. The injector system of Claim 62 wherein the fluid comprises a contrast agent.

64. The injector system of Claim 63 wherein the contrast agent comprises an ultrasound contrast agent.

65. The injector system of Claim 62 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

66. The injector system of Claim 62 wherein the at least one agitation element comprises a solid.

67. The injector system of Claim 66 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

68. The injector system of Claim 62 wherein the at least one agitation element comprises a gas.

69. The injector system of Claim 62 wherein the movement mechanism moves the syringe in one or more of circular, partially circular and linear motions.

70. The injector system of Claim 62 wherein the movement mechanism moves the syringe in a rotational motion.

71. The injector system of Claim 70 wherein the axis of rotation is variable.

72. The injector system of Claim 68 wherein the at least one agitation element is surrounded by a cover.

73. The injector system of Claim 62, further comprising a recess defined in at least one of the body of the syringe and the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

74. The injector system of Claim 73 wherein the recess is defined in the body of the syringe adjacent to the distal discharge end thereof.

75. The injector system of Claim 73 wherein the recess is defined in the plunger of the syringe

76. The injector system of Claim 73 wherein the recess comprises an annular recess.

77. An injector system comprising:  
an injector comprising a syringe mounting device;  
a syringe comprising:

a body comprising a distal discharge end and an injector attachment device cooperable with the syringe mounting device for mounting the syringe on the injector;

a plunger movably disposed within the body; and

at least one agitation element disposed within the body between the plunger and the distal discharge end; and

a movement mechanism operably associated with the injector, the movement mechanism operable to rotate the syringe such that the at least one agitation element agitates a fluid contained in the syringe.

78. The injector system of Claim 77 wherein the fluid comprises a contrast agent.



79. The injector system of Claim 78 wherein the contrast agent comprises an ultrasound contrast agent.

80. The injector system of Claim 77 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

81. The injector system of Claim 77 wherein the at least one agitation element comprises a solid.

82. The injector system of Claim 81 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

83. The injector system of Claim 77 wherein the at least one agitation element comprises a gas.

84. The injector system of Claim 77 wherein the movement mechanism is further operable to move the syringe in one or more of circular, partially circular and linear motions.

85. The injector system of Claim 77 wherein the axis of rotation is variable.

86. The injector system of Claim 83 wherein the at least one agitation element is surrounded by a cover.

87. The injector system of Claim 77, further comprising a recess defined in at least one of the body of the syringe and the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

88. The injector system of Claim 87 wherein the recess is defined in the body of the syringe adjacent to the distal discharge end thereof.

89. The injector system of Claim 87 wherein the recess is defined in the plunger of the syringe

90. The injector system of Claim 87 wherein the recess comprises an annular recess.

91. An injector system comprising:  
an injector comprising a syringe mounting device;  
a syringe comprising:

a body comprising a distal discharge end, an injector attachment device cooperable with the syringe mounting device for mounting the syringe on the injector, and a recess defined therein;

a plunger movably disposed within the body; and

at least one agitation element disposed within the body between the plunger and the distal discharge end, the recess operable to accommodate the at least one agitation element; and

a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe.

92. The injector system of Claim 91 wherein the fluid comprises a contrast agent.

93. The injector system of Claim 92 wherein the contrast agent comprises an ultrasound contrast agent.

94. The injector system of Claim 91 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

95. The injector system of Claim 91 wherein the at least one agitation element comprises a solid.

96. The injector system of Claim 95 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

97. The injector system of Claim 91 wherein the at least one agitation element comprises a gas.

98. The injector system of Claim 91 wherein the movement mechanism moves the syringe in one or more of circular, partially circular and linear motions.

99. The injector system of Claim 91 wherein the movement mechanism moves the syringe in a rotational motion.

100. The injector system of Claim 99 wherein the axis of rotation is variable.

101. The injector system of Claim 97 wherein the at least one agitation element is surrounded by a cover.

102. The injector system of Claim 91 wherein the recess is located adjacent to the distal discharge end of the syringe.

103. The injector system of Claim 91 wherein the recess comprises an annular recess.

104. A method for agitating the contents of a syringe comprising a body having a distal discharge end, a plunger movably disposed within the body and at least one agitation element disposed within the body between the plunger and the distal discharge end, the method comprising:

providing a movement mechanism operably associated with an injector to which the syringe is mounted, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe;

activating the movement mechanism to move the syringe; and  
agitating the fluid in the syringe with the at least one agitation element.

105. The method of Claim 104, further comprising:  
deactivating the movement mechanism to terminate the agitation of the  
syringe contents.

106. The method of Claim 104 wherein the contents of the syringe  
comprise a contrast agent.

107. The method of Claim 104 wherein the movement mechanism rotates  
the syringe.

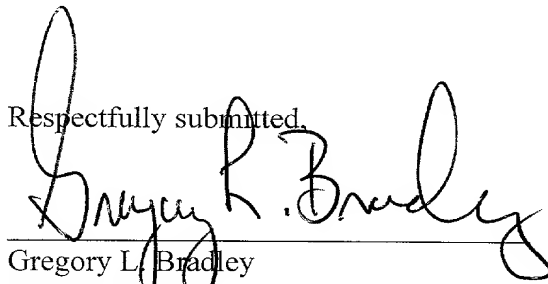
108. The method of Claim 107 wherein the axis of rotation is variable.

109. The method of Claim 104 wherein the syringe further comprises a  
recess defined in at least one of the body of the syringe and the plunger of the  
syringe, the recess operable to accommodate the at least one agitation element.

110. The method of Claim 109 wherein the recess is defined in the body of  
the syringe adjacent to the distal discharge end thereof.

111. The method of Claim 109 wherein the recess comprises an annular  
recess. --

Respectfully submitted,



Gregory L. Bradley  
Reg. No. 34,299

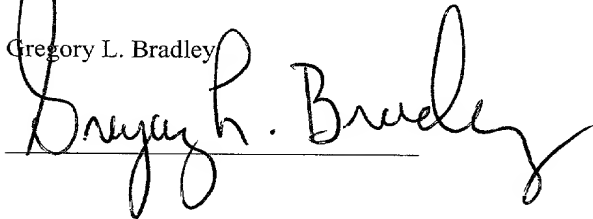
Dated: February 26, 2001

Medrad, Inc.  
One Medrad Drive  
Indianola, PA 15051  
Telephone: (412) 767-2400 ext. 3021

CERTIFICATE OF EXPRESS MAILING

"Express Mail" Mailing Label No. EL623140254US. Date of Deposit: February 26, 2001. I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service "Express Mail Post Office To Addressee" Service under 37 C.F.R. 1.10 on the date indicated above and is addressed to: Box PCT, Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Gregory L. Bradley

A handwritten signature in black ink, reading "Gregory L. Bradley", written over a horizontal line.

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APPENDIX OF PENDING CLAIMS 1-33 AND NEW CLAIMS 34-111

1. A syringe for use with an injector having a movement mechanism operably associated therewith, the syringe comprising:

a body comprising a distal discharge end;

a plunger movably disposed within the body; and

at least one agitation element disposed within the body between the plunger and the distal discharge end, the at least one agitation element operable to agitate a fluid in the syringe when the syringe is moved with respect to gravity by means of the movement mechanism operably associated with the injector.

2. The syringe of Claim 1 wherein the fluid comprises a contrast agent.

3. The syringe of Claim 2 wherein the contrast agent comprises an ultrasound contrast agent.

4. The syringe of Claim 1 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

5. The syringe of Claim 1 wherein the at least one agitation element comprises a solid.

6. The syringe of Claim 5 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

7. The syringe of Claim 1 wherein the at least one agitation element comprises a gas.

8. The syringe of Claim 1 wherein the movement mechanism operably associated with the injector is operable to move the syringe in one or more of circular, partially circular and linear motions.

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9. The syringe of Claim 1 wherein the movement mechanism operably associated with the injector is operable to move the syringe in a rotational motion.

10. The syringe of Claim 9 wherein the axis of rotation is variable.

11. The syringe of Claim 1 wherein the at least one agitation element comprises a casing.

12. The syringe of Claim 7 wherein the at least one agitation element is surrounded by a cover.

13. The syringe of Claim 1, further comprising a recess defined in the body of the syringe, the recess operable to accommodate the at least one agitation element.

14. The syringe of Claim 13 wherein the recess is defined adjacent to the distal discharge end of the syringe.

15. The syringe of Claim 1, further comprising a recess defined in the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

16. The syringe of Claims 13-15 wherein the recess comprises an annular recess.

17. An injector system comprising:  
an injector comprising means for mounting a syringe thereon;  
a syringe comprising a body having a distal discharge end and means cooperable with the injector means for mounting the syringe on the injector, a plunger movably disposed within the body, and at least one agitation element disposed within the body between the plunger and the distal discharge end; and

a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe.

18. The injector system of Claim 17 wherein the fluid comprises a contrast agent.

19. The injector system of Claim 18 wherein the contrast agent comprises an ultrasound contrast agent.

20. The injector system of Claim 17 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

21. The injector system of Claim 17 wherein the at least one agitation element comprises a solid.

22. The injector system of Claim 21 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

23. The injector system of Claim 17 wherein the at least one agitation element comprises a gas.

24. The injector system of Claim 17 wherein the movement mechanism moves the syringe in one or more of circular, partially circular and linear motions.

25. The injector system of Claim 17 wherein the movement mechanism moves the syringe in a rotational motion.

26. The injector system of Claim 25 wherein the axis of rotation is variable.



27. The injector system of Claim 23 wherein the at least one agitation element is surrounded by a cover.

28. The injector system of Claim 17, further comprising a recess defined in the body of the syringe, the recess operable to accommodate the at least one agitation element.

29. The injector system of Claim 28 wherein the recess is defined adjacent to the distal discharge end of the syringe.

30. The injector system of Claim 17, further comprising a recess defined in the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

31. The injector system of Claims 28-30 wherein the recess comprises an annular recess.

32. A method for agitating the contents of a syringe, comprising:  
providing an injector comprising means for mounting a syringe thereon;  
providing a syringe comprising a body having a distal discharge end and means cooperable with the injector means for mounting the syringe on the injector, a plunger movably disposed within the body, and at least one agitation element disposed within the body between the plunger and the distal discharge end;  
providing a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe;  
activating the movement mechanism to move the syringe; and  
agitating the fluid in the syringe with the at least one agitation element.

33. The method of Claim 32, further comprising the step of deactivating the movement mechanism to terminate the agitation of the syringe contents.

34. A syringe for use with an injector having a movement mechanism operably associated therewith, the syringe comprising:

a body comprising a distal discharge end;

a plunger movably disposed within the body; and

at least one agitation element disposed within the body between the plunger and the distal discharge end, the at least one agitation element operable to agitate a fluid in the syringe when the syringe is rotated by means of the movement mechanism.

35. The syringe of Claim 34 wherein the fluid comprises a contrast agent.

36. The syringe of Claim 35 wherein the contrast agent comprises an ultrasound contrast agent.

37. The syringe of Claim 34 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

38. The syringe of Claim 34 wherein the at least one agitation element comprises a solid.

39. The syringe of Claim 38 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

40. The syringe of Claim 34 wherein the at least one agitation element comprises a gas.

41. The syringe of Claim 34 wherein the movement mechanism operably associated with the injector is further operable to move the syringe in one or more of circular, partially circular and linear motions.

42. The syringe of Claim 34 wherein the axis of rotation is variable.

43. The syringe of Claim 34 wherein the at least one agitation element comprises a casing.

44. The syringe of Claim 40 wherein the at least one agitation element is surrounded by a cover.

45. The syringe of Claim 34, further comprising a recess defined in at least one of the body of the syringe and the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

46. The syringe of Claim 45 wherein the recess is defined in the body of the syringe adjacent to the distal discharge end thereof.

47. The syringe of Claim 45 wherein the recess is defined in the plunger of the syringe.

48. The syringe of Claim 45 wherein the recess comprises an annular recess.

49. A syringe for use with an injector having a movement mechanism operably associated therewith, the syringe comprising:

a body comprising a distal discharge end;

a plunger movably disposed within the body;

at least one agitation element disposed within the body between the plunger and the distal discharge end, the at least one agitation element operable to agitate a fluid in the syringe when the syringe is moved with respect to gravity by means of the movement mechanism; and

a recess defined in the body of the syringe, the recess operable to accommodate the at least one agitation element.

50. The syringe of Claim 49 wherein the fluid comprises a contrast agent.

51. The syringe of Claim 50 wherein the contrast agent comprises an ultrasound contrast agent.

52. The syringe of Claim 49 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

53. The syringe of Claim 49 wherein the at least one agitation element comprises a solid.

54. The syringe of Claim 53 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

55. The syringe of Claim 49 wherein the at least one agitation element comprises a gas.

56. The syringe of Claim 49 wherein the movement mechanism operably associated with the injector is operable to move the syringe in one or more of circular, partially circular and linear motions.

57. The syringe of Claim 49 wherein the movement mechanism operably associated with the injector is operable to move the syringe in a rotational motion.

58. The syringe of Claim 57 wherein the axis of rotation is variable.

59. The syringe of Claim 49 wherein the at least one agitation element comprises a casing.

60. The syringe of Claim 55 wherein the at least one agitation element is surrounded by a cover.

61. The syringe of Claim 49 wherein the recess comprises an annular recess.

62. An injector system comprising:

an injector comprising a syringe mounting device;

a syringe comprising:

a body comprising a distal discharge end and an injector attachment device cooperable with the syringe mounting device for mounting the syringe on the injector;

a plunger movably disposed within the body; and

at least one agitation element disposed within the body between the plunger and the distal discharge end; and

a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe.

63. The injector system of Claim 62 wherein the fluid comprises a contrast agent.

64. The injector system of Claim 63 wherein the contrast agent comprises an ultrasound contrast agent.

65. The injector system of Claim 62 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

66. The injector system of Claim 62 wherein the at least one agitation element comprises a solid.

67. The injector system of Claim 66 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

68. The injector system of Claim 62 wherein the at least one agitation element comprises a gas.

69. The injector system of Claim 62 wherein the movement mechanism moves the syringe in one or more of circular, partially circular and linear motions.

70. The injector system of Claim 62 wherein the movement mechanism moves the syringe in a rotational motion.

71. The injector system of Claim 70 wherein the axis of rotation is variable.

72. The injector system of Claim 68 wherein the at least one agitation element is surrounded by a cover.

73. The injector system of Claim 62, further comprising a recess defined in at least one of the body of the syringe and the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

74. The injector system of Claim 73 wherein the recess is defined in the body of the syringe adjacent to the distal discharge end thereof.

75. The injector system of Claim 73 wherein the recess is defined in the plunger of the syringe

76. The injector system of Claim 73 wherein the recess comprises an annular recess.

77. An injector system comprising:  
an injector comprising a syringe mounting device;  
a syringe comprising:  
a body comprising a distal discharge end and an injector attachment device cooperable with the syringe mounting device for mounting the syringe on the injector;  
a plunger movably disposed within the body; and

at least one agitation element disposed within the body between the plunger and the distal discharge end; and

a movement mechanism operably associated with the injector, the movement mechanism operable to rotate the syringe such that the at least one agitation element agitates a fluid contained in the syringe.

78. The injector system of Claim 77 wherein the fluid comprises a contrast agent.

79. The injector system of Claim 78 wherein the contrast agent comprises an ultrasound contrast agent.

80. The injector system of Claim 77 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

81. The injector system of Claim 77 wherein the at least one agitation element comprises a solid.

82. The injector system of Claim 81 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

83. The injector system of Claim 77 wherein the at least one agitation element comprises a gas.

84. The injector system of Claim 77 wherein the movement mechanism is further operable to move the syringe in one or more of circular, partially circular and linear motions.

85. The injector system of Claim 77 wherein the axis of rotation is variable.

86. The injector system of Claim 83 wherein the at least one agitation element is surrounded by a cover.

87. The injector system of Claim 77, further comprising a recess defined in at least one of the body of the syringe and the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

88. The injector system of Claim 87 wherein the recess is defined in the body of the syringe adjacent to the distal discharge end thereof.

89. The injector system of Claim 87 wherein the recess is defined in the plunger of the syringe

90. The injector system of Claim 87 wherein the recess comprises an annular recess.

91. An injector system comprising:  
an injector comprising a syringe mounting device;  
a syringe comprising:  
a body comprising a distal discharge end, an injector attachment device cooperable with the syringe mounting device for mounting the syringe on the injector, and a recess defined therein;  
a plunger movably disposed within the body; and  
at least one agitation element disposed within the body between the plunger and the distal discharge end, the recess operable to accommodate the at least one agitation element; and  
a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe.

92. The injector system of Claim 91 wherein the fluid comprises a contrast agent.



93. The injector system of Claim 92 wherein the contrast agent comprises an ultrasound contrast agent.

94. The injector system of Claim 91 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

95. The injector system of Claim 91 wherein the at least one agitation element comprises a solid.

96. The injector system of Claim 95 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

97. The injector system of Claim 91 wherein the at least one agitation element comprises a gas.

98. The injector system of Claim 91 wherein the movement mechanism moves the syringe in one or more of circular, partially circular and linear motions.

99. The injector system of Claim 91 wherein the movement mechanism moves the syringe in a rotational motion.

100. The injector system of Claim 99 wherein the axis of rotation is variable.

101. The injector system of Claim 97 wherein the at least one agitation element is surrounded by a cover.

102. The injector system of Claim 91 wherein the recess is located adjacent to the distal discharge end of the syringe.

103. The injector system of Claim 91 wherein the recess comprises an annular recess.

104. A method for agitating the contents of a syringe comprising a body having a distal discharge end, a plunger movably disposed within the body and at least one agitation element disposed within the body between the plunger and the distal discharge end, the method comprising:

providing a movement mechanism operably associated with an injector to which the syringe is mounted, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe;

activating the movement mechanism to move the syringe; and

agitating the fluid in the syringe with the at least one agitation element.

105. The method of Claim 104, further comprising:

deactivating the movement mechanism to terminate the agitation of the syringe contents.

106. The method of Claim 104 wherein the contents of the syringe comprise a contrast agent.

107. The method of Claim 104 wherein the movement mechanism rotates the syringe.

108. The method of Claim 107 wherein the axis of rotation is variable.

109. The method of Claim 104 wherein the syringe further comprises a recess defined in at least one of the body of the syringe and the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

110. The method of Claim 109 wherein the recess is defined in the body of the syringe adjacent to the distal discharge end thereof.

111. The method of Claim 109 wherein the recess comprises an annular recess.

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## **SYRINGES AND INJECTORS INCORPORATING MECHANICAL FLUID AGITATION DEVICES**

### **Background of the Invention**

5           The present invention relates generally to movement devices for agitating the contents of syringes and, more particularly, to syringes and injectors incorporating movement devices for agitating contrast agents disposed within the syringes.

10           Syringes which are prefilled with ultrasound contrast agents are clamped into injectors for injection. The syringes remain therein for several minutes to one or more hours. The duration of one or more injections, including the intervening periods between the injections, may last for more than 10  
15 minutes. Depending on the nature and composition of the contrast agent, dissociation commences at different times. During this period, the ultrasound contrast agent becomes dissociated and the phases are separated from one another. The ultrasound contrast agent as a whole is no longer homogeneous. In order to restore this homogeneity, the entire injector, including the syringe  
20 clamped therein, is moved manually. Movements of this nature are not reproducible, and sufficient homogenization is not ensured.

          Ultrasound contrast agents are sensitive to transverse forces. Under excessively high forces, the particles are torn apart and destroyed. This  
25 impairs the quality of the ultrasound contrast agent. Thus, to maintain the suspension of particles in ultrasound contrast agents it is necessary to agitate the agents, but at the same time the particles must not be destroyed by the agitation.

30           Ultrasound contrast agents are generally described in Supplement to Diagnostic Imaging, May 1995, Advanced Ultrasound, Editor: Peter L. OGLE, Editorial Offices: 600 Harrison St. San Francisco, CA 94107 USA.

Glass syringes and plastic syringes are described extensively in the publication by Junga (M. JUNG (1973) Pharm. Ind. Vol. 35, No. 11a, pages 824 to 829). A mixture of glass and plastic is described in PCT Publication No. WO 96/00098.

5

Injectors are generally described in EP Publication No. 0 584 531.

### Summary of the Invention

10

The present invention provides apparatuses and methods for maintaining the homogeneity and integrity of an ultrasound contrast agent over a relatively long period of time without destroying the consistency of the ultrasound contrast agent and hence impairing its pharmacological and diagnostic properties. The dissociation begins immediately after the initial preparation of the ultrasound contrast agent, and at the latest after the syringe has been inserted into the injector when the latter is at rest (i.e., is not moving). By maintaining the homogeneity and integrity of the particles suspended in the contrast agent at optimal levels, the diagnostic properties of the contrast agent can be optimized.

20

The present invention further provides apparatuses and methods for continuous, controlled and/or reproducible agitation procedures for contrast agents. These procedures can be utilized between the time of preparation of the contrast agents and their injection into a patient.

25

Further, the present invention provides agitation procedures that can be specifically designed and/or adjusted for specific contrast agents, including ultrasound contrast agents.

30

Also, the agitation procedures may be designed to minimize turbulent agitation of the contrast agents, thereby reducing shear forces and other stresses that could be harmful to the integrity of the particles suspended in the contrast agents.

Moreover, the present invention provides a controlled application of magnetic energy to maintain the homogeneity of the contrast agent suspension, without mixing or otherwise destroying the particles of the contrast agents.

One aspect of the present invention is achieved by means of a syringe which is filled with ultrasound contrast agent for administering the contents thereof by means of an injector, wherein at least one agitation element is contained in the syringe. The agitation element can be present as a solid or a gas, and preferably has a different density from that of the ultrasound contrast agent. Preferably, the syringe is movable with respect to the lines of gravity by means of the injector or an accessory thereto.

Another aspect of the present invention is achieved by means of an injector, or an accessory therefore, that moves a syringe mounted thereon for inducing at least one agitation element disposed within the syringe to agitate the contents thereof. The at least one agitation element may be present in the syringe in a solid or a gas phase, and preferably has a density different from that of the ultrasound contrast agent.

In a preferred embodiment, the movements of the syringe are circular, partially circular or linear. The movements of the syringe must be such that the agitation element disposed within the syringe moves with respect thereto. Typical movements contemplated by the present invention include pitching, swaying, yawing and shaking. All linear movements with a horizontal vector are also included. Movements along the lines of gravity typically do not induce any mixing or homogenization of the contrast agent contained within the syringe. Only when a movement component which does not run exclusively along the lines of gravity is added does homogenization of the contrast agent become possible. Preferably, the movements are rotational movements, the axis of rotation of which may be arranged as desired.

In a preferred embodiment, the present invention provides a combination of a syringe filled with a contrast agent and an injector or an accessory for use with an injector. At least one agitation element is contained in the syringe, is present as a gas or a solid and has a density different from that of the contrast fluid. The syringe is movable with respect to the lines of gravity by means of the injector or the accessory therefore.

Preferably, the syringes are made from plastic, glass or plastic/glass. Furthermore, the syringe are preferably disposable syringes.

The agitation element may be a gas or a solid body, the density of which differs from that of the ultrasound contrast agent. Preferably, the agitation element comprises a solid body with a density that is higher than that of the ultrasound contrast agent. The agitation element can move in the syringe under the force of gravity, by the syringe being moved about, for example, one of its axes.

To accomplish this movement, the injector adjusts and/or moves the syringe by means of a tilting movement with respect to the longitudinal axis thereof. Preferably, the injector is mounted in such a way that the mounted, approximately horizontally-arranged syringe is moved about this position, the center of rotation preferably lying outside the syringe and the axis of rotation being perpendicular to the longitudinal axis of the syringe.

The present invention, along with further aspects and attendant advantages, will best be understood by reference to the following detailed description taken in conjunction with the accompanying drawings.

### Brief Description of the Drawings

30

Figure 1 is an elevated, cross-sectional view of an injector system incorporating a rotation device between the injector stand and the injector housing.

Figure 2 is an elevated, cross-sectional view of an injector system incorporating an accessory for tilting the injector and syringe mounted thereon.

5           Figure 3 is a graphical view comparing the Doppler signal intensity of a contrast agent with resuspension versus that of the contrast agent with no resuspension.

10           Figure 4 is a graphical view comparing the Doppler signal intensity of a contrast agent with resuspension versus that of the contrast agent with no resuspension.

15           Figure 5 is a graphical view comparing the Doppler signal intensity of a contrast agent with no resuspension versus that of the contrast agent with low-speed and high-speed resuspensions.

20           Figure 6 is a graphical view comparing the Doppler signal intensity of a contrast agent with medium vibratory resuspension versus that of the contrast agent with no resuspension.



## Detailed Description of the Presently Preferred Embodiments

Before turning to a detailed description of the preferred embodiments, as illustrated in Figures 1 and 2, the present invention is described first below in general terms applicable to all suitable embodiments thereof.

As an initial matter, the terms "syringe" and/or "syringes" as used herein can mean and encompass the following terms and devices: cartridges (large-volume syringe with a volume of at least 100 ml); ampoule syringes; disposable syringes; disposable syringe ampoules; throw-away syringe ampoules; throw-away syringes; injection ampoules; disposable injection ampoules; ready-for-injection ampoules; cylindrical ampoules; twin-chamber injection ampoules; two-chamber syringes; two-chamber syringe ampoules; and no-delay syringes.

In addition, the terms "injector" and/or "injectors" as used herein can mean and encompass the following terms and devices: infusion pumps; infusers; perfusers; and all other applicators or devices that operate to empty syringes of fluid contain therein.

Further, the terms "accessory" and/or "accessories" as used herein can mean and encompass the following: all devices which are or may be physically connected to an injector and assume the role of moving the entire injector or parts thereof in such a way that the syringe changes position. Typical accessories include tables which execute a wobbling movement or a rocking movement and on which the injectors are positioned. Further accessories may include a shaft, for example, a motor-drive shaft, that is attached to the stand of the injector and changes the position of the syringe. In this case, the syringe, a holder for the syringe, the ram and the ram-moving device (e.g., a motor) are usually rigidly connected to one another. The essential factor is that the injector or the accessory therefor moves at least the syringe with respect to the standing surface or suspension mount of the injector or of the accessory.

In the present invention, the agitation element may be encased by various substances. Suitable substances for the casing include, but are not limited to, glass and plastic materials, such as Teflon, which are preferably inert with respect to contrast agents. The use of a casing also reduces friction, which results in a reduction in or avoidance of particles within the syringe. Preferably, the agitation element is in the form of a ball. It is also possible for the gas to be surrounded by a cover, as is found with floats or immersed bodies.

The syringe preferably includes a recess therein for accommodating the agitation element. The recess preferably is designed in such a way that the agitation element can slide into or out of the recess. The recess preferably lies outside the movement range of the plunger in the syringe or itself forms part of the plunger.

Also, the recess may be formed both in the syringe and in the plunger. Preferably, the recess is positioned at or adjacent to the distal end (i.e., the syringe end having the needle attachment, hose attachment or luer lock fitting) of the syringe.

Further, the recess may be situated in the distal cover of the syringe cylinder or located in the syringe cylinder itself, close to the cover. In this case, a lock is preferably included to prevent the agitation element from blocking the syringe outlet.

In addition, the recess may comprise an annular recess that is disposed in the cover of the syringe cylinder. This design eliminates the need to orient the agitation element with respect to the syringe when the latter has been completely emptied.

Preferably, the recess is arranged in the syringe plunger. In this case, careful attention should be paid to the accurate orientation of the plunger with respect to the magnetic field source, unless an annular recess is situated in that part of the plunger which faces toward the needle attachment end (i.e.,

distal end) of the syringe. Combinations of recesses on the plunger and, at the same time, at that end of the syringe which lies at the needle attachment are also conceivable.

5           An important feature of the syringe is the design of the plunger, the closure, and the corresponding distal opening.

10           The agitation element must be controlled in such a way that sufficient homogenization is ensured but the particles in the ultrasound contrast agent are not destroyed by transverse forces. The intensity and frequency of the movement has to be controlled, in accordance with the sensitivity of the ultrasound contrast agent and in accordance with the movement sequence, in such a way that the consistency of the particles in the ultrasound contrast agent is not adversely affected.

15           Turning now to the drawings of the preferred embodiments, Figure 1 illustrates a syringe 1 having a plunger 2 movably disposed therein and a needle attachment or distal discharge end 3. The syringe 1 is removably connected to an injector 5 via a holder 4. Therefore, the syringe 1 can be  
20           inserted into the holder 4 in a reversible manner.

25           The injector 5 has a ram 6 which is removably connected to the plunger 2 of the syringe 1. The ram 6 is moved with respect to the housing of the injector 5 by a motor 7, the motor turning a ring 8 which has a screw thread and surrounds the ram 6, which likewise has a complementary screw thread. The ring 8 is rotatable with respect to the housing.

30           The housing of the injector 5 is connected to the stand 10 of the injector 5 via a joint 9. A rocker motor 11 allows relative movement between housing of the injector 5 and its stand 10. The movement of the rocker motor 11 is controlled by a control device 12. It is possible here to account individually for the nature of the contrast agent, the size of the syringe, the volume per minute of the injection and the stress of the patient.

At or near the distal end of the syringe 1, the syringe 1 includes a recess 13 for accommodating an agitation element 14, which is preferably in the form of a ball. Shortly before the syringe 1 has been completely emptied of its contents, the control device 12 adjusts the position of the syringe 1 in such a way that the ball 14 slides into the recess 13, thereby allowing the plunger 2 to be driven completely to the end of the syringe 1 in the direction of the needle attachment end 3 thereof.

Figure 2 illustrates a syringe 1 having a plunger 2 movably disposed therein and a needle attachment or distal discharge end 3. The syringe 1 is removably connected to an injector 5 via a holder 4. Therefore, the syringe 1 can be inserted into the holder 4 in a reversible manner.

The injector 5 includes a ram 6 which is removably connected to the plunger 2 of the syringe 1. The ram 6 is moved with respect to the housing of the injector 5 by a motor 7, the motor turning a ring 8 which has a screw thread and surrounds the ram 6, which likewise has a complementary screw thread. The ring 8 is rotatable with respect to the housing.

The injector 5, as shown, preferably stands on an accessory 15 for the injector. This accessory 15 has a stand base 16 and a stand surface 17 which is connected to the stand base 16 via a pivot joint 18. A lifting motor 19 moves a linkage 20 which is designed in the form of scissors and is connected to the motor via a connecting rod 21. The movement is controlled by means of a control device 12.

In the end of the plunger 2 facing the distal discharge end 3 of the syringe 1, the plunger 2 includes a plunger recess 22 for accommodating an agitation element 14, which is preferably in the form of a ball. Shortly before the syringe 1 has been completely emptied of its contents, the control device 12 adjusts the position of the syringe 1 in such a way that the ball 14 slides into the

plunger recess 22, thereby allowing the plunger 2 to be driven completely in the direction of the needle attachment 3 end thereof.

## Examples

5

### Example 1

A vibratory agitator was used to prevent phase separation in Levovist™ ultrasound contrast agent. The vibratory agitator includes a motor-driven vibrating unit and an electronic control unit containing a battery supply and controls for regulating the degree of vibration. The vibrating unit was connected mechanically to the syringe.

At low concentrations (e.g., 200 mg/ml), Levovist™ does not remain stable as a suspension for longer than 2-3 minutes. The suspension separates into two different phases: a liquid phase (which forms on the top of the agent) and a particle phase (which collects at the bottom). After resuspension, however, Levovist™ still provides optimal clinical results.

At a concentration of 300 mg/ml, Levovist™ separates into phases after 25-30 minutes, well above the Levovist™ approval limit of 10-15 minutes. At a concentration of 400 mg/ml, Levovist™ separates only after a matter of hours. Thus, for concentrations of 300 mg/ml and 400 mg/ml, no additional agitation is required to maintain Levovist™ in solution.

25

### Test Setup

The vibratory agitator was tested with a 200 mg/ml concentration of Levovist™ using in-vitro Doppler measurement equipment. An IVAC P400 pump and a 20-ml Levovist™ syringe, which was connected directly to the vibratory agitator. To avoid vibration power loss, the pump's syringe holder was not connected to the syringe.

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## Testing Method

The trial consisted of three separate examinations without vibration and three with medium vibration power. The infusion flow settings were between 100 and 200 ml/h. Different flow settings only lead to differences in the achievable Doppler intensity, not to differences in the (qualitative) curve form.

## Test Results

Figure 6 illustrates the results of the tests in graphical form, which plots Doppler intensity (dB) versus time (Sec.). The graph in Figure 6 shows (1) three trials without vibration; and (2) three trials with a constant medium vibration.

Without vibration, the typical suspension problems with Levovist™ at a concentration of 200 mg/ml are shown in Figure 6. It is not possible to obtain a constant plateau phase of Doppler intensity. All of the non-vibration curves have more than one local maximum over time. Curve 3 does have a plateau, but only for one minute and at a low intensity level.

With vibration, plateau phases were achieved for the following durations: (1) Curve 1 – 2 minutes (70-190 sec.); (2) Curve 2 – 1.5 minutes (90-180 sec.); and (3) Curve 3 – 3 minutes (120-300 sec.).

However, the vibratory agitator did not provide a complete constant Doppler intensity plateau. In the vibratory curves, a second maximum with too strong an increase in Doppler intensity was observed. For example, second maximums occurred at the following times: (1) Curve 1 – at 300 sec. and at plus 10dB compared to the prior level; (2) Curve 2 – at 200 sec. and at plus 8dB compared to the prior level; and (3) Curve 3 – at 350 sec. and at plus 14dB compared to the prior level.

## Example 2

The below examples use magnetic bars and ferromagnetic balls driven by a magnetic field to agitate or resuspend the contrast agents. While the examples do not use the mechanical devices disclosed herein, the results of increased and/or consistent enhancement properties for agitated or resuspended contrast agents may be considered independent of the means used to agitate or resuspend the contrast agents.

For Levovist™ 200 mg/ml ultrasound contrast fluid, which is manufactured by Schering AG of Berlin, Germany, phase separation occurs within a couple of minutes (approximately 3-5 minutes) after preparation. This phase separation is characterized by contrast particles aggregating at the lower part of a syringe containing the contrast fluid and the watery diluent collecting above the contrast particles within the syringe.

A number of technical approaches to mitigating and/or preventing Levovist™ phase separation were tested using a standardized laboratory model. In the first technical approach, a small ferromagnetic ball (having a higher specific weight than Levovist™) was placed in a syringe and moved therein by means of a magnetic field applied thereto. In the second technical approach, an agitation element (having a higher specific weight than Levovist™) was placed in the syringe and moved therein by means of an external magnetic bar moved outside of and relative to the syringe.

### Test Setup

The tests were conducted using in-vitro test equipment validated to simulate in-vivo contrast enhancement conditions. The test equipment allowed reproducible measurements of the enhancement characteristics of ultrasound contrast fluid suspensions.

Through the controlled movement or control of a magnetic field source, agitation elements placed in the syringe were able to be moved in a

controlled fashion to agitate the ultrasound contrast fluid to prevent phase separation. After agitation, the ultrasound contrast fluid was injected into the testing equipment using a transfer tube and a 22G needle. The simulated body temperature was 37°C and the simulated negative pressure of the lung  
5 simulating component (i.e., oxygenator) of the testing equipment was 100 mBar.

### Testing Method

Respective measurements of the enhancement properties of the  
10 ultrasound contrast fluid suspension over a prolonged period of time (up to 22 minutes) were conducted for syringes having magnetic agitation elements and for syringes not incorporating magnetic agitation elements. A standard infusion / injection speed of 1 ml/min was used throughout the tests. The impact of the phase separation mitigation approaches were deducted from the variances in  
15 the measured Doppler-signal intensity.

### Test Results – Test One

As shown in Figure 3, no agitation of the ultrasound contrast fluid  
20 suspension leads to significant unfavorable inconsistencies in the enhancement properties of the contrast fluid, which is not suitable for clinical applications. However, when a magnetic bar was used to agitate the ultrasound contrast fluid suspension within the syringe, by means of a magnetic source located outside of the syringe, the contrast fluid was resuspended and a long-lasting, stable  
25 enhancement pattern was achieved.

### Test Results – Test Two

In this test, a ferromagnetic ball was moved within the syringe  
30 through application of an outside magnetic field. Again, as shown in Figure 4, the test results clearly indicate that resuspension of the ultrasound contrast fluid suspension leads to significantly more consistent enhancement properties when compared to non-resuspended ultrasound contrast fluid suspension. With



regard to the non-resuspended contrast fluid enhancement properties, the differences compared to Results – Test One (above) show that the extent and impact of phase separation on contrast enhancement is largely unpredictable.

5           Test Results – Test Three

In this test, a magnetic bar was moved within the syringe through application of a ferromagnetic object outside the syringe. Besides a baseline comparison (i.e., compared to no resuspension of contrast fluid suspension),  
10   the influence of variations in the strength of the mechanical forces for resuspension were investigated. As can be clearly deduced from the test results, as shown in Figure 5, ultrasound contrast fluid suspensions contain fragile particles and the mechanical forces applied for resuspension must therefore be adjusted to the stability and strength of the contrast fluid  
15   suspension. An extremely vigorous resuspension is detrimental for the enhancement properties of the contrast fluid, whereas a slight agitation may not prevent phase separation. The key is to adjust the resuspension mode in way that the forces impacting the contrast fluid particles do not impair or limit their contrast enhancement purpose. The level of mechanical force required and/or  
20   tolerable for each individual ultrasound contrast fluid, including Levovist™ varies, but a reproducible and controllable resuspension mode is required.

It should be appreciated that the present invention may be configured as appropriate for the application. The embodiments described  
25   above are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is indicated by the following claims, rather than by the foregoing description. All changes which fall within the meaning and range of equivalency of the claims are to be embraced within their scope.

**List of reference numerals:**

- 1 Syringe
- 2 Plunger
- 5 3 Needle attachment
- 4 Holder
- 5 Injector
- 6 Ram
- 7 Motor
- 10 8 Ring
- 9 Joint
- 10 Stand foot
- 11 Rocker motor
- 12 Control device
- 15 13 Bulge
- 14 Ball
- 15 Accessory
- 16 Stand base
- 17 Stand surface
- 20 18 Pivot joint
- 19 Lifting motor
- 20 Linkage
- 21 Connecting rod
- 22 Plunger bulge

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**WHAT IS CLAIMED IS:**

1. A syringe for use with an injector having a movement mechanism operably associated therewith, the syringe comprising:

- 5       a body comprising a distal discharge end;  
      a plunger movably disposed within the body; and  
      at least one agitation element disposed within the body between the plunger and the distal discharge end, the at least one agitation element operable to agitate a fluid in the syringe when the syringe is moved with respect to gravity  
10      by means of the movement mechanism operably associated with the injector.

2. The syringe of Claim 1 wherein the fluid comprises a contrast agent.

- 15      3. The syringe of Claim 2 wherein the contrast agent comprises an ultrasound contrast agent.

20      4. The syringe of Claim 1 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

5. The syringe of Claim 1 wherein the at least one agitation element comprises a solid.

25      6. The syringe of Claim 5 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

7. The syringe of Claim 1 wherein the at least one agitation element comprises a gas.

30      8. The syringe of Claim 1 wherein the movement mechanism operably associated with the injector is operable to move the syringe in one or more of circular, partially circular and linear motions.

9. The syringe of Claim 1 wherein the movement mechanism operably associated with the injector is operable to move the syringe in a rotational motion.

5 10. The syringe of Claim 9 wherein the axis of rotation is variable.

11. The syringe of Claim 1 wherein the at least one agitation element comprises a casing.

10 12. The syringe of Claim 7 wherein the at least one agitation element is surrounded by a cover.

13. The syringe of Claim 1, further comprising a recess defined in the body of the syringe, the recess operable to accommodate the at least one  
15 agitation element.

14. The syringe of Claim 13 wherein the recess is defined adjacent to the distal discharge end of the syringe.

20 15. The syringe of Claim 1, further comprising a recess defined in the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

25 16. The syringe of Claims 13-15 wherein the recess comprises an annular recess.

17. An injector system comprising:  
an injector comprising means for mounting a syringe thereon;  
a syringe comprising a body having a distal discharge end and means  
30 cooperable with the injector means for mounting the syringe on the injector, a plunger movably disposed within the body, and at least one agitation element disposed within the body between the plunger and the distal discharge end; and

a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe.

5           18. The injector system of Claim 17 wherein the fluid comprises a contrast agent.

10           19. The injector system of Claim 18 wherein the contrast agent comprises an ultrasound contrast agent.

15           20. The injector system of Claim 17 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

20           21. The injector system of Claim 17 wherein the at least one agitation element comprises a solid.

25           22. The injector system of Claim 21 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

30           23. The injector system of Claim 17 wherein the at least one agitation element comprises a gas.

          24. The injector system of Claim 17 wherein the movement mechanism moves the syringe in one or more of circular, partially circular and linear motions.

          25. The injector system of Claim 17 wherein the movement mechanism moves the syringe in a rotational motion.

          26. The injector system of Claim 25 wherein the axis of rotation is variable.

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27. The injector system of Claim 23 wherein the at least one agitation element is surrounded by a cover.

28. The injector system of Claim 17, further comprising a recess defined in the body of the syringe, the recess operable to accommodate the at least one agitation element.

29. The injector system of Claim 28 wherein the recess is defined adjacent to the distal discharge end of the syringe.

30. The injector system of Claim 17, further comprising a recess defined in the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

31. The injector system of Claims 28-30 wherein the recess comprises an annular recess.

32. A method for agitating the contents of a syringe, comprising:  
providing an injector comprising means for mounting a syringe thereon;  
providing a syringe comprising a body having a distal discharge end and means cooperable with the injector means for mounting the syringe on the injector, a plunger movably disposed within the body, and at least one agitation element disposed within the body between the plunger and the distal discharge end;

providing a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe;

activating the movement mechanism to move the syringe; and  
agitating the fluid in the syringe with the at least one agitation element.

33. The method of Claim 32, further comprising the step of deactivating the movement mechanism to terminate the agitation of the syringe contents.

TOP SECRET

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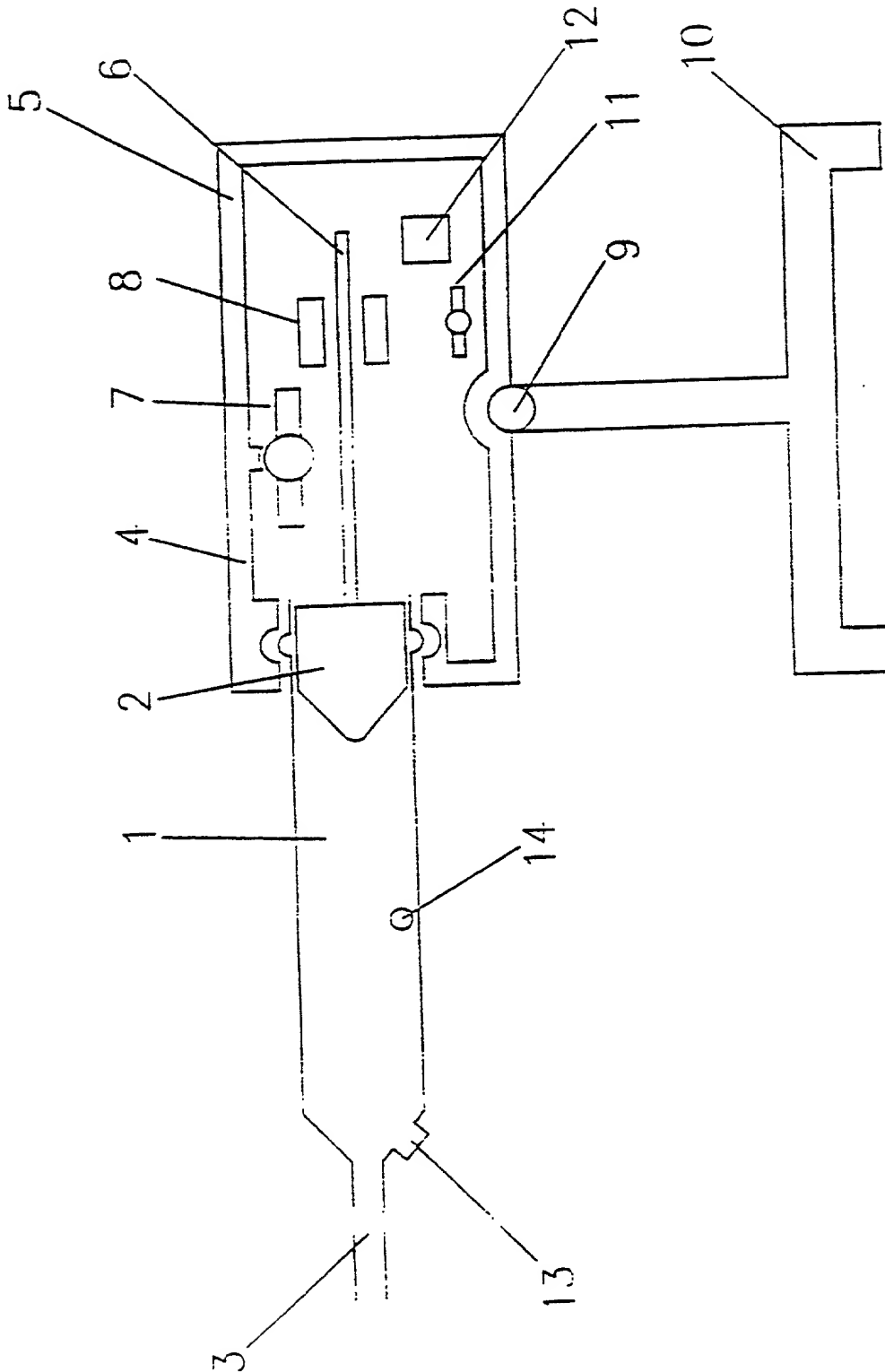


Figure 1

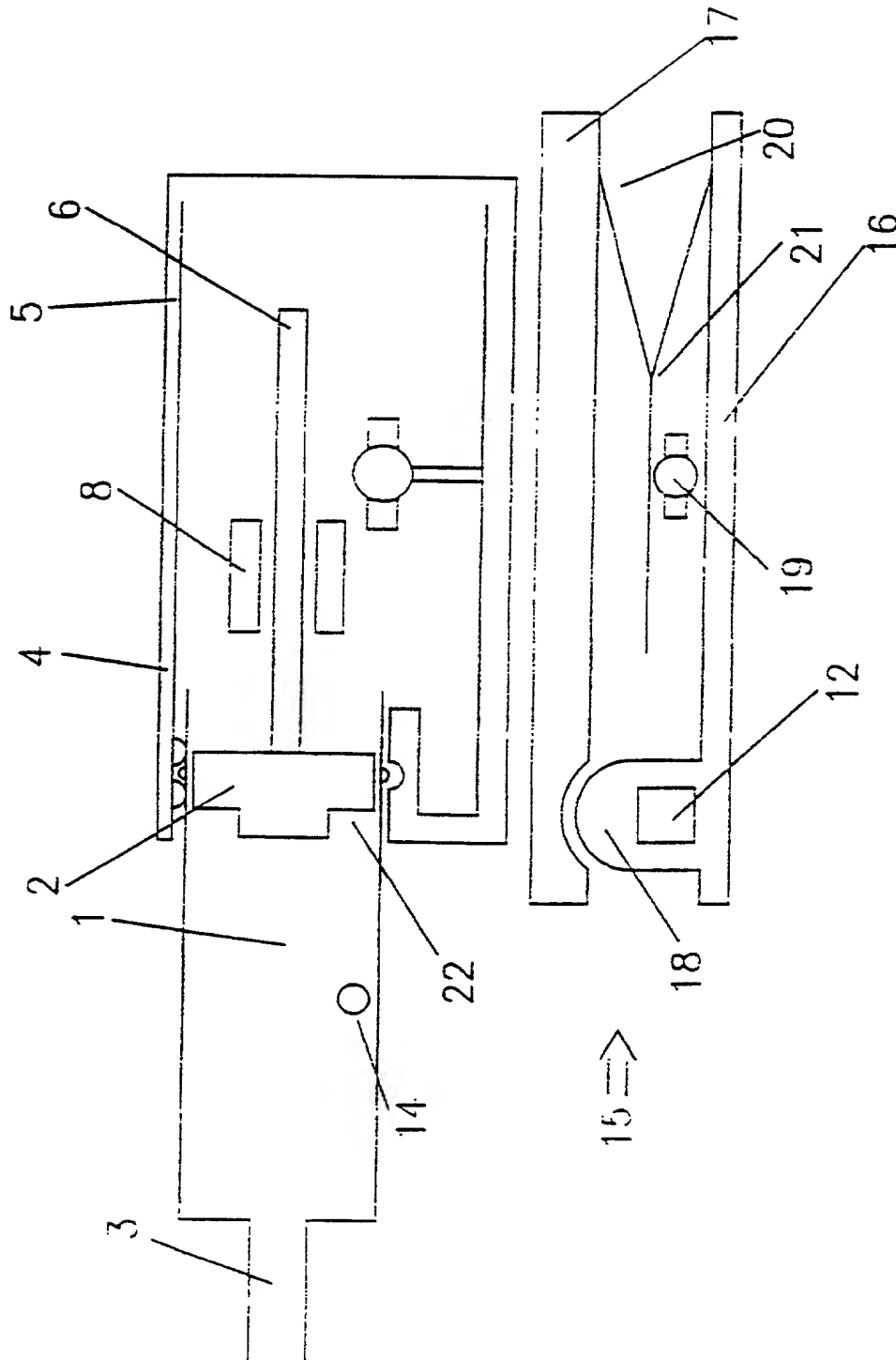


Figure 2



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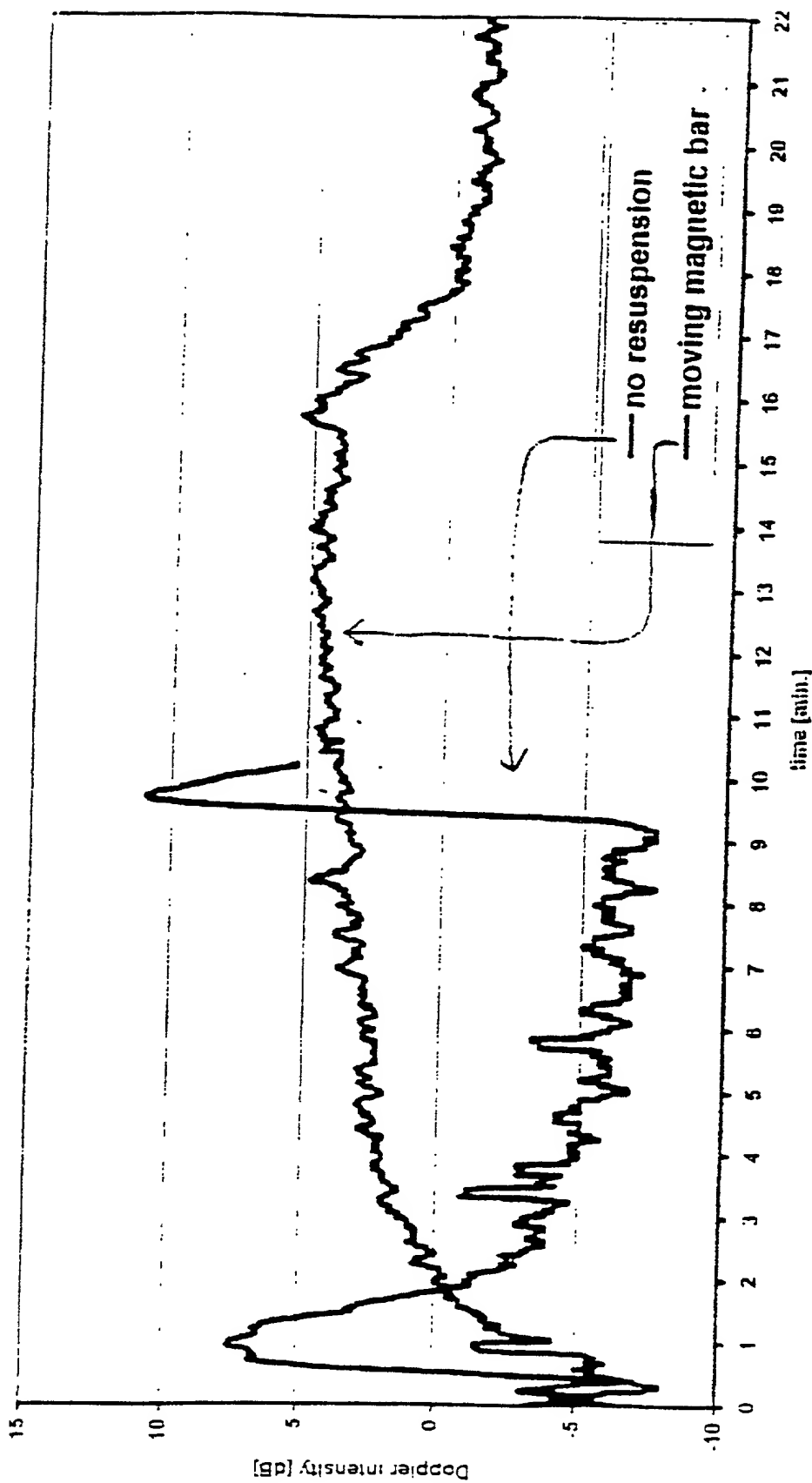


Figure 3

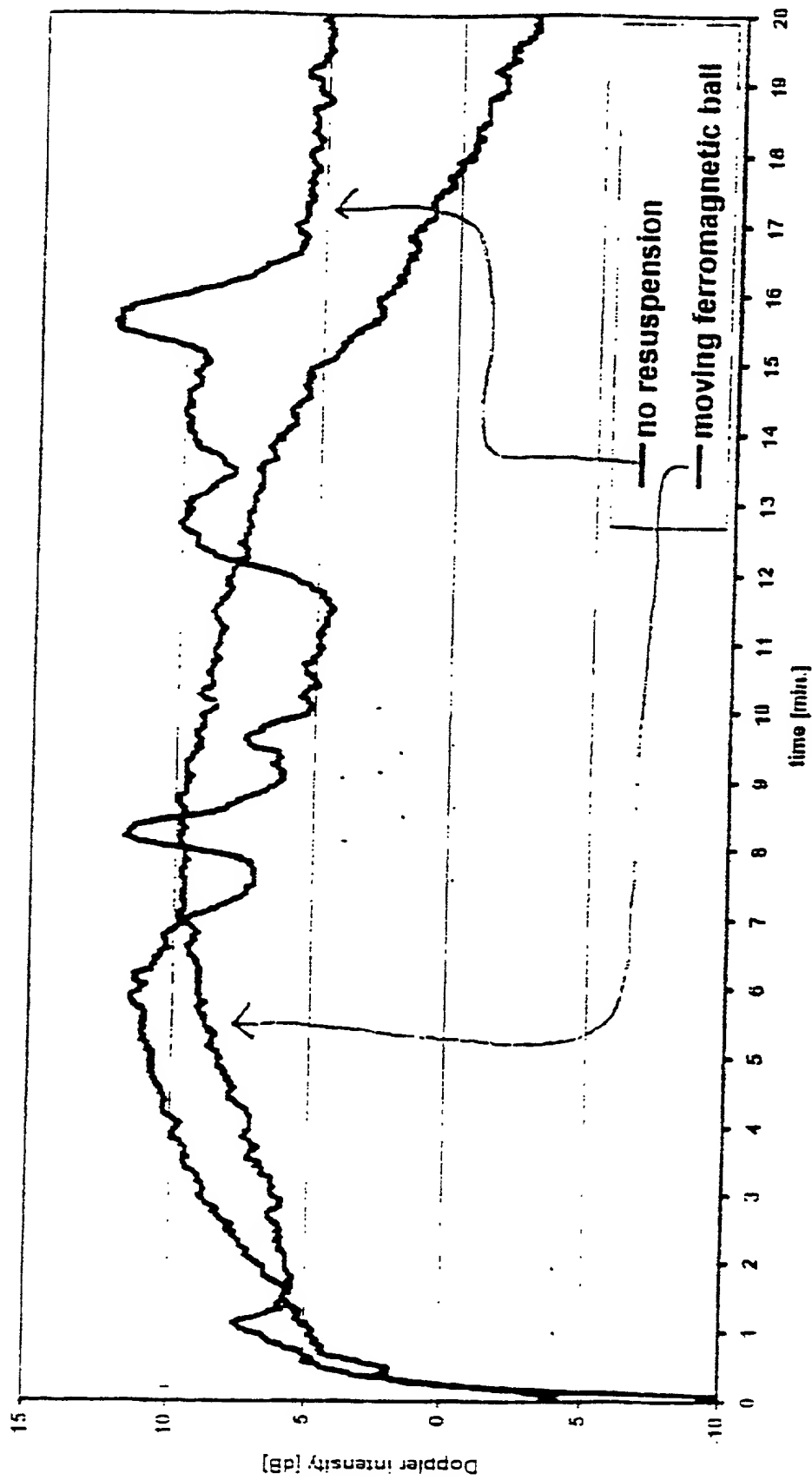


Figure 4

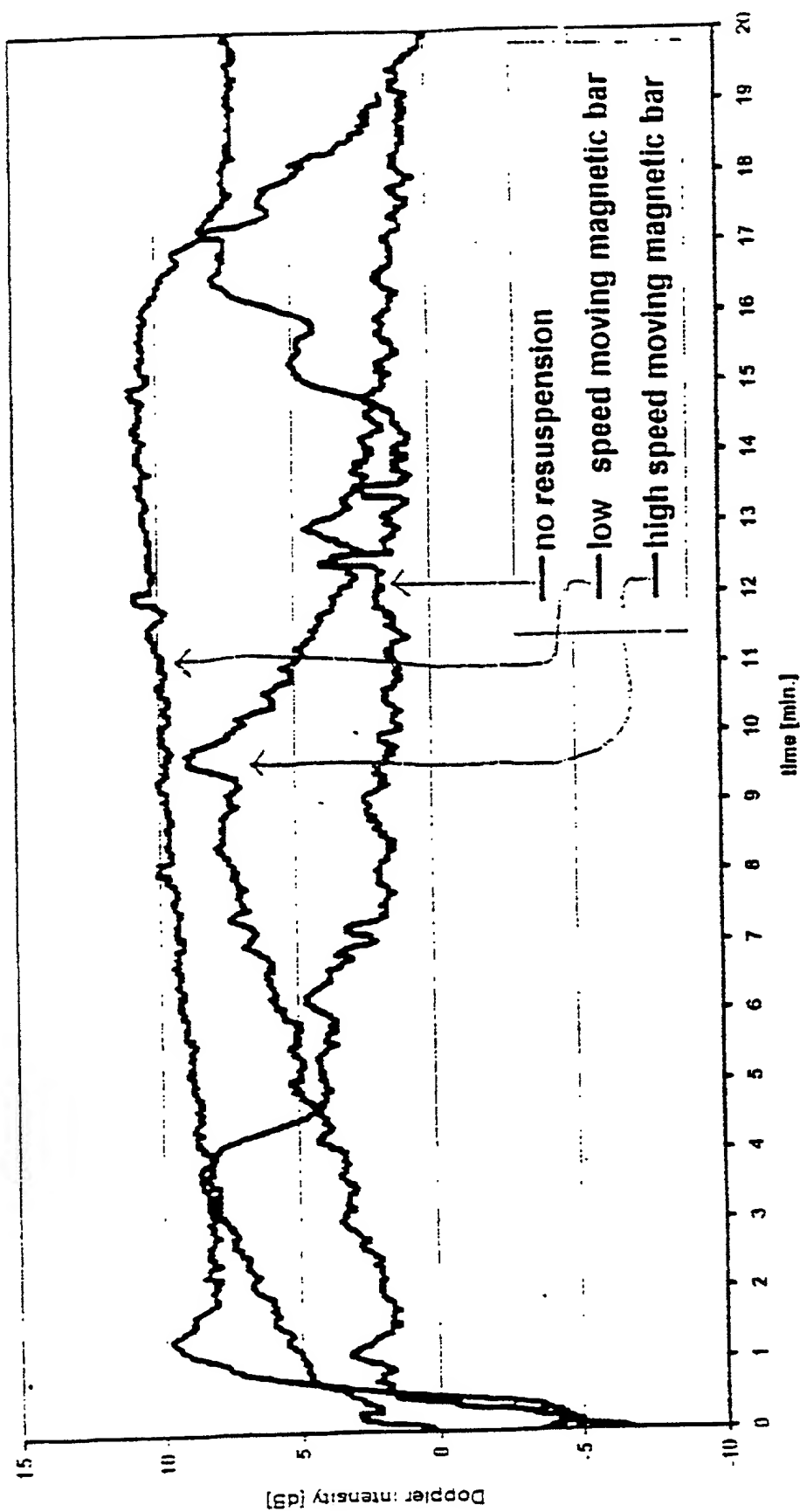


Figure 5

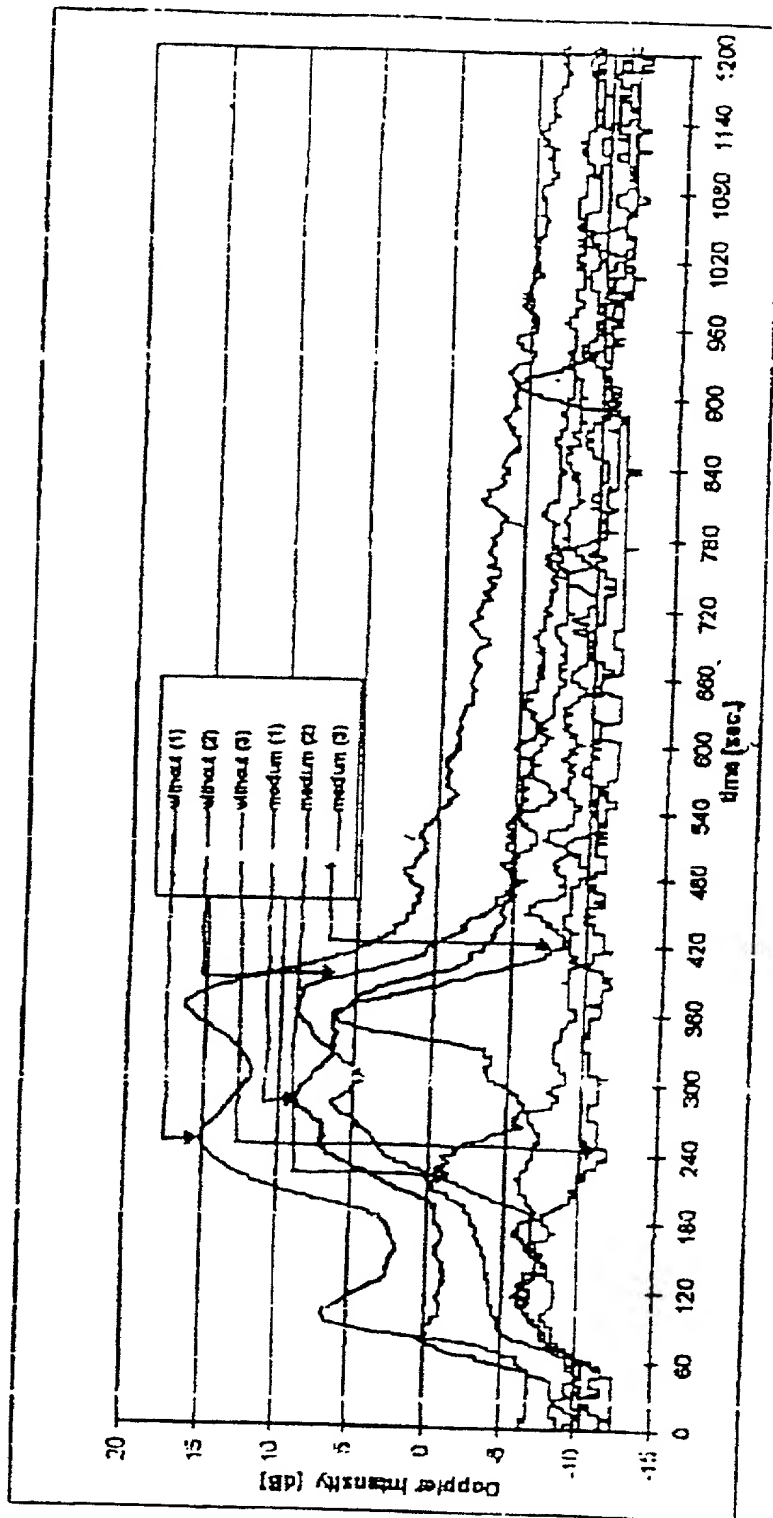


Figure 6

Docket No.  
VI/98-023.DE.PCT.US

## Declaration and Power of Attorney For Patent Application

### English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**SYRINGES AND INJECTORS INCORPORATING MECHANICAL FLUID AGITATION DEVICES** ✓

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on 8/26/1999 ✓ as United States Application No. or PCT International Application Number PCT/EP99/06290 ✓ and was amended on \_\_\_\_\_ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

|                                   |                               |   |
|-----------------------------------|-------------------------------|---|
| <u>198 40 532.4</u> ✓<br>(Number) | <u>Germany</u> ✓<br>(Country) | <u>28/08/1998</u> ✓<br>(Day/Month/Year Filed) |
| _____<br>(Number)                 | _____<br>(Country)            | _____<br>(Day/Month/Year Filed)               |
| _____<br>(Number)                 | _____<br>(Country)            | _____<br>(Day/Month/Year Filed)               |

☐☐☐

13/06

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

13/06

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

1-00 Gregory L. Bradley, Reg. No. 34, 299

Send Correspondence to: Gregory L. Bradley  
Medrad, Inc.  
One Medrad Drive  
Indianola, PA 15051

Direct Telephone Calls to: (name and telephone number)  
Gregory L. Bradley, (412) 767-2400

Full name of sole or first inventor

URICH, Klaus

Sole or first inventor's signature

Date

13/06/01

Residence

Berlin, Germany DEX

Citizenship

German ✓

Post Office Address

Parkstraße 27a

13129 Berlin, Germany

Full name of second inventor, if any

Second inventor's signature

Date

Residence

Citizenship

Post Office Address

13/06